CONFORMATIONAL ANALYSIS OF 2-ARYL-4-PIPERIDONES. EFFECT OF THE INDOLE PROTECTIVE PHENYLSULFONYL GROUP

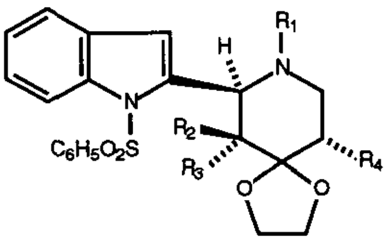
Mario Rubiralta,[a,*] Javier Luque,[b] Modesto Orozco,[c] Anna Diez,[a] and Isabel López[a]

[a] Laboratory of Organic Chemistry, Faculty of Pharmacy; [b] Laboratory of Physical Chemistry, Faculty of Pharmacy; [c] Department of Biochemistry and Physiology, Faculty of Chemistry, University of Barcelona, 08028 Barcelona, Spain

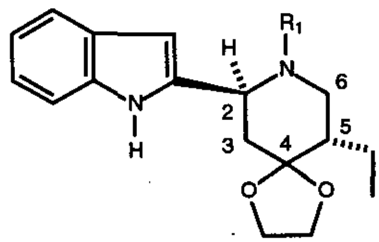
Abstract – A spectroscopic and theoretical study on 2-arylpiperidines, which shows a rare stabilization in an axial disposition of the aryl substituent in the particular cases of 2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidones (**11**) and (**12**), is reported.

2-Aryl-4-piperidones are valuable synthetic intermediates of alkaloid analogues and potential pharmacologically active compounds.[1] In previous works we have reported some aspects of the conformational analysis of 2-aryl-4-piperidones related to the restricted rotation of the C_2-Ar bond by nmr spectroscopy[2] and MM2 calculations.[3] Recently, we have also used several 2-indolyl-4-piperidones and their ethylene acetals as key intermediates in the synthesis of indole alkaloids related compounds.[4-7] One of the most characteristic spectroscopic features of 2-indolylpiperidines is the methine proton at the C-2 position. Thus, the C-2 methine proton appears at δ 4.16 for secondary piperidine acetal (**14**), at δ 4.22 and 3.92 for the *N*-methyl derivatives (**5**) and (**6**), respectively, and at δ 4.10 and 3.40 for indole deprotected compounds (**7**) and (**8**), respectively (see Table 1). These differences of chemical shifts are due to the shielding effect promoted by the alkylation upon the nitrogen atom and by the deshielding effect due to the electron-withdrawing character of the phenylsulfonyl group. In all cases the coupling constants (*ca.*

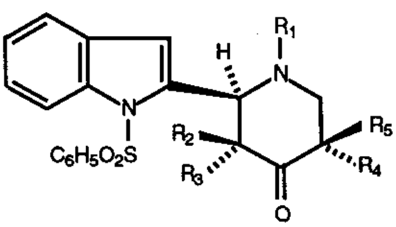
12 and 3 Hz) are indicative of an axial disposition of the C-2 methine proton, and by extension the more stable equatorial orientation for the indolyl group is demonstrated (see Table 1). However, when we prepared the corresponding 4-piperidones such as **9** and **12**,[4] we observed that this proton was more deshielded than in the ethylenedioxy acetals (δ~4.7 for **9** and δ~4.9 for **12**) and showed unexpected coupling constants (*ca.* 4–6 Hz). This fact prompted us to prepare the simplified piperidone (**11**)[8] by hydrolysis of acetal (**5**).[9] The ^{1}H nmr spectrum of **11** showed a triplet at δ 4.70 with a coupling constant of 6 Hz, which demonstrated the equatorial disposition of the C-2 proton, and hence, the axial orientation of the 1-(phenylsulfonyl)-2-indolyl group.



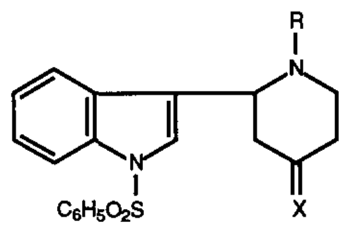
1 $R_1=R_2=R_3=R_4=H$
2 $R_1=R_3=R_4=H$; $R_2=C_2H_5$
3 $R_1=R_2=R_4=H$; $R_3=C_2H_5$
4 $R_1=R_2=R_3=H$; $R_4=C_2H_5$
5 $R_1=CH_3$; $R_2=R_3=R_4=H$
6 $R_1=CH_3$; $R_4=C_2H_5$; $R_2=R_3=H$



7 $R_1=H$
8 $R_1=CH_3$



9 $R_1=R_2=R_4=R_5=H$; $R_3=C_2H_5$
10 $R_1=R_3=R_4=R_5=H$; $R_2=C_2H_5$
11 $R_1=CH_3$; $R_2=R_3=R_4=R_5=H$
12 $R_1=CH_3$; $R_2=R_3=R_4=H$; $R_5=C_2H_5$
13 $R_1=CH_3$; $R_2=R_3=R_5=H$; $R_4=C_2H_5$



14 $R=H$; $X=OCH_2CH_2O$
15 $R=CH_3$; $X=OCH_2CH_2O$
16 $R=CH_3$; $X=O$

Figure 1

Table 1. ^{1}H Nmr (200 MHz) chemical shifts in $CDCl_3$ of 2-H in 2-indolyl-4-piperidones (**9-13**) and their ethylene acetals (**1-8** and **14-16**).

Compound	Chemical Shifts (δ)	Multiplicity	Coupling Constant (Hz)
1	4.50	dd	12 and 3
2	4.90	d	2
3	4.42	d	12
4	4.54	dd	12 and 2.4
5	4.22	dd	11 and 2.9
6	3.92	dd	12.9 and 2.7
7	4.10	dd	12 and 2.4
8	3.40	dd	10.4 and 4.6
9	4.68	d	4.3
10	5.12	d	7
11	4.70	t	6
12	4.92	dd	6 and 4
13	4.36	dd	11.2 and 4.2
14	4.16	dd	11 and 3
15	3.43	dd	11.5 and 2.7
16	3.59	dd	11 and 3

In Figure 2 we show the ring inversion equilibrium of both piperidones and their ethylene acetals. In the latter, when the indolyl group is in an axial disposition it presents 1,3-diaxial interactions with the axial C-O bond at the C-4 position and in minor extension with the axial C-6 protons, which promote the equilibrium shift towards conformer A. Nevertheless, in the D conformation of 4-piperidones, the carbonyl group avoids the destabilizing 1,3-diaxial interactions. However, since the preference for conformer D had not been experimentally observed by nmr spectroscopy in indolylpiperidines lacking the phenylsulfonyl group, nor in 2-phenyl-4-piperidones, we thought of a stabilizing effect of such protective group.

In order to evaluate if the variation of the substitution position of the indole ring system on the piperidine provoked a modification of the phenylsulfonyl group effect, piperidines (**15**) and (**16**) were prepared by methylation of **14** and further deprotection of the carbonyl group in 4 *N* hydrochloric acid. As expected, piperidine (**15**)[10] showed a doublet-of-doublets at δ 3.43 for the C-2 proton with coupling constants of 11.5 and 2.7 Hz, characteristic of an A conformation. Piperidone (**16**)[11] showed similar coupling constants, thus indicating a C conformation. This result made clear that only when the piperidine ring was substituted on the C-2 position of the indole system, a large contribution of conformation D was observed.

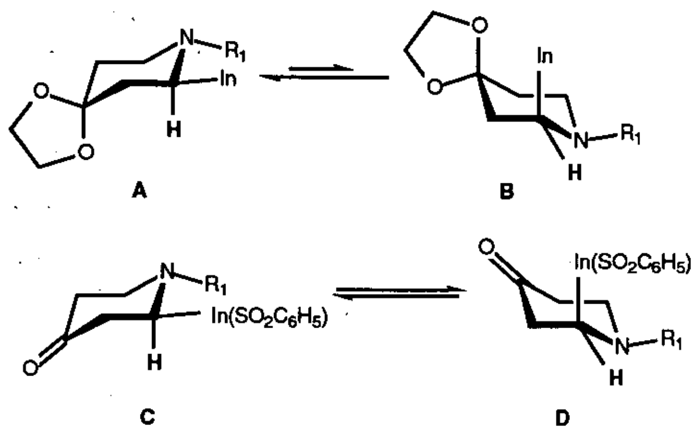


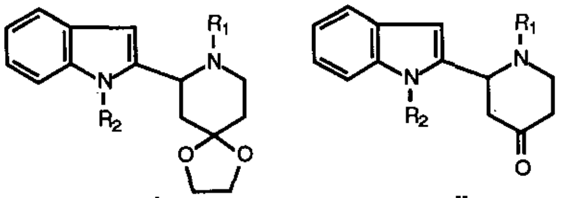
Figure 2

In order to find an explanation for the rare stabilization of this aryl group in an axial disposition, energy minimizations of several simplified 2-indolyl-4-piperidones and their 4,4-ethylenedioxy derivatives were performed using the program DISCOVER .[12-14] Energy minimizations were run only considering chair conformations of B (or D, axial aryl substituent) and of A (or C, equatorial aryl substituent) of each compound. In Table 2 the calculated energy differences between axial and equatorial aryl conformers are shown (E_{ax}-E_{eq}), as an indication of which of the conformers is favored for each compound. Thus, the first striking feature is the negative value of such difference in compounds (**11**) and (**19**), meaning a more stable axial conformation, which is in perfect accordance with the previous nmr observations. The energy difference (E_{ax}-E_{eq}, Table 2) for ketones is much smaller than in acetals as a consequence of the lack of 1,3-diaxial interactions in the former. However, the introduction of a phenylsulfonyl group increases such an energy difference about 2 Kcal mol^{-1} in all cases, due to the major steric hindrance provoked.

In all cases, the most stable conformation obtained theoretically shows the indolyl group almost perpendicular to the piperidine ring [dihedral angles N_a-C2-InC2-N_b: -134.6° for **1**; -132.4 for **5**; -150.2° for **19**-(*C*); -71.0° for **19**-(*D*); -139.4° for **11**-(*C*); and -107.2° for **11**-

(*D*)]. It is interesting to note that the folding of the phenylsulfonyl group for compound (**11**) changes toward the opposite site of the *N*-methyl substituent when the indolyl group adopts the axial conformation (see Figure 3).

Table 2. Relative energy for all chair conformers of 2-(2-indolyl)piperidines.



I II

Compound		R_1	R_2	E_{ax}-E_{eq} (Kcal/mol)	Most stable conformer
I:	**1**	H	$SO_2C_6H_5$	4.30	A (eq)
	5	CH_3	$SO_2C_6H_5$	4.41	A (eq)
	17	H	H	2.04	A (eq)
	18	CH_3	H	2.27	A (eq)
II:	**11**	CH_3	$SO_2C_6H_5$	-0.49	D (ax)
	19	H	$SO_2C_6H_5$	-0.31	D (ax)
	20	CH_3	H	1.24	C (eq)
	21	H	H	1.56	C (eq)

Conclusion

Both experimental and theoretical considerations have demonstrated the existence of an unusual stabilization of the aryl substituent in the axial disposition for 2-[1-(phenylsulfonyl)-2-indolyl)piperidines. Such stabilization can be understood from the compromise between 1,3-diaxial interactions of the aryl substituent and the axial group in position 4, and the steric hindrance originated by the introduction of the protective phenylsulfonyl group.

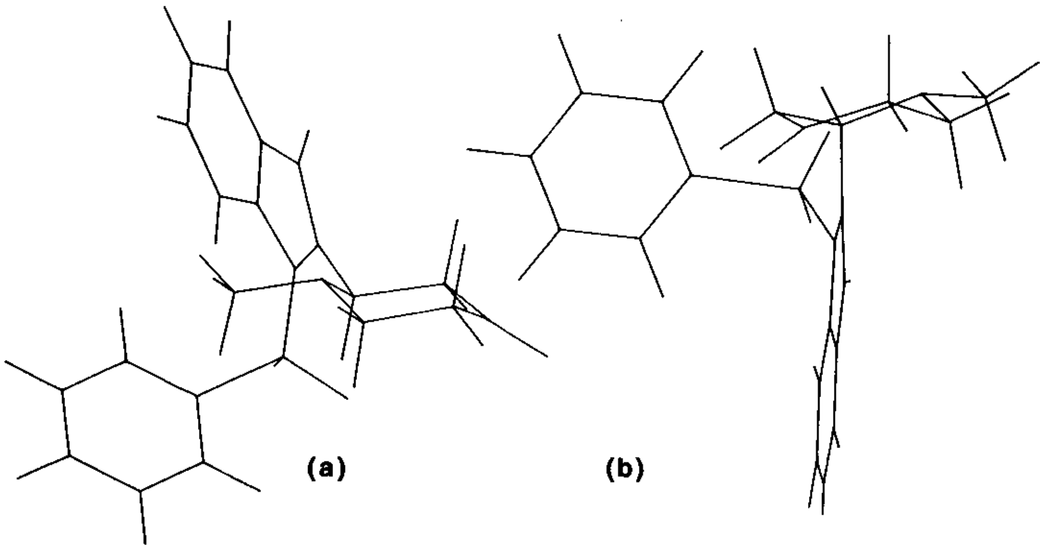


Figure 3. Representation of the conformations of the global minimum energy of 1-methyl-2-[1-(phenylsulfonyl)-2-indolyl]-4-piperidone (**11**) obtained from computer simulation. a) Conformation with the indole group in an equatorial position. b) Conformation with the indole group in an axial position.

Computer Simulations

Energy minimizations were performed with the force-field CVFF[12,13] implemented in the program DISCOVER[14] on an Iris System (Silicon Graphics). A harmonic potential for bond streching and a scaling factor of 0.25 for 1-4 interactions were used in calculations. Cross-tem energy contributions were also taken into account. The default dielectric constant of 1.0 was used for all calculations. Energy minimizations were performed with a conjugate gradient method until the maximum derivative was less than 0.001 Kcal/mol· Å.

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8. **11**: Ir ($CHCl_3$) 1716 (C=O); ^1H nmr (200 MHz) 2.20 (s, 3H, NCH_3), 2.44 (br t, J = 6 Hz, 1H, 5-Ha), 2.72 (dd, J = 13, 6 Hz, 1H, 3-Ha), 4.70 (t, J = 6 Hz, 1H, 2-He), 6.63 (s, 1H, In-3H), 7.15-7.50 (m, 7H , ArH), 7.78 (d, J = 7 Hz, 1H, In-4H), 8.25 (d, J = 7 Hz, 1H, In-7H); ^{13}C nmr 38.8 (C-5), 40.1 (NCH_3), 44.0 (C-3), 51.1 (C-6), 58.7 (C-2), 110.5 (In-C7), 114.9 (In-C3), 120.9 (In-C4), 123.7 (In-C5), 124.9 (In-C6), 126.0 (Ar-*ortho*), 128.8 (Ar-*meta*), 133.6 (Ar-*para*), 137.1 (In-C7a), 139.7 (C-*ipso*), 141.3 (In-C2), 208.1 (C=O); ms (m/z, %) 368 (M^+, 31), 353 (11), 283 (7), 227 (100%, M^+-$SO_2C_6H_5$), 170 (16), 143 (26), 84 (92), 58 (53). Anal. Calcd for $C_{20}H_{20}N_2O_3S \cdot H_2O$: C, 62.17; H, 5.69; N, 7.25; S, 8.28. Found: C, 62.14, H, 5.41; N, 7.00; S, 8.06.
9. **5**: Hydrochloride mp 249-250 °C (acetone); ^1H nmr 1.78 (t, J = 11 Hz, 1H, 3-Ha), 1.85 (m, 2H, 3-He and 5-He), 1.99 (s, 3H, NCH_3), 2.08 (td, J = 12, 5 Hz, 1H, 5-Ha), 2.60 (td, J = 12, 2.5 Hz, 1H, 6-Ha), 3.00 (br d, J = 12 Hz, 1H, 6-He), 3.80-4.10 (m, 4H, OCH_2), 4.22 (dd, J = 11, 2.9 Hz, 1H, 2-Ha), 6.81 (s, 1H, In-3H), 7.20-7.50 (m, 6H), 7.80 (d, J = 7 Hz, 2H), 8.32 (d, J = 7 Hz, 1H); ^{13}C nmr 34.2 (C-5), 42.0 (C-3), 42.1 (NCH_3), 54.0 (C-6), 58.8 (C-2), 64.2 (OCH_2), 106.5 (C-4), 110.0 (In-C3), 114.9 (In-C7), 120.8

(In-C5), 123.7 (In-C4), 124.6 (In-C6), 126.5 (Ar-*ortho*), 129.2 (Ar-*meta*), 129.4 (In-C3a), 133.9 (Ar-*para*), 135.5 (In-C7a), 139.5 (Ar-*ipso*), 142.4 (In-C2). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.05; H, 5.86; N, 6.79. Found: C, 64.00; H, 5.90; N, 6.80.

10. **15**: Ir ($CHCl_3$) 1223 (C-O); ^1H nmr (200 MHz) 1.76 (br d, J = 13 Hz, 1H, 3-He), 1.95 (s, 3H, NCH_3), 2.44 (td, J = 13, 2 Hz, 1H, 6-Ha), 2.96 (dm, J = 13 Hz, 1H, 6-He), 3.40 (dd, J = 13, 2 Hz, 1H, 2-Ha), 7.16-7.50 (m, 6H, ArH), 7.52 (s, 1H, In-2H), 7.83 and 7,84 (2 d, J = 7 Hz, 1H each, In-4H and Ar-*ortho*), 7.98 (d, J = 7 Hz, 1H, In-7H); ^{13}C nmr 34.6 (C-5), 41.7 (C-3), 42.9 (NCH_3), 54.0 (C-6), 59.1 (C-2), 64.1 (OCH_2), 106.9 (C-4), 113.6 (In-C7), 120.8 (In-C4), 123.2 (In-C5), 123.7 (In-C2), 124.9 (In-C6), 126.6 (Ar-*ortho*), 129.2 (Ar-*meta*), 129.4 (In-C3a), 133.8 (Ar-*para*), 135.2 (In-C7a), 137.9 (In-C3); ms (m/z, %) 412 (M^+, 47), 369 (11), 283 (12), 271 (100), 241 (12), 214 (25), 185 (45), 142 (48), 115 (31), 86 (38), 77 (54). Anal. Calcd for $C_{22}H_{24}N_2O_4S$: C, 64.06; H 5.86, N, 6.79. Found: C, 64.35; H, 5.52; N, 7.06.

11. **16**: mp 136-137 °C (acetone); ir ($CHCl_3$) 1715 (C=O); ^1H nmr (200 MHz) 2.10 (s, 3H, NCH_3), 2.43 (dd, J = 12, 3 Hz, 1H, 3-He), 2.55 (dd, J = 12, 4 Hz, 1H, 5-He), 2.70-2.85 (t, J = 12 Hz, 1H, 6-Ha), 3.14-3.25 (m, 1H, 6-He), 3.59 (dd, J = 12, 3 Hz, 1H, 2-Ha), 7.15-7.50 (m, 6H, ArH), 7.42 (s, 1H, In-2H), 7.85 (d, J = 7 Hz, 2H, In-4H and Ar-*ortho*), 8.00 (d, J = 7 Hz, 1H, In-7H); ^{13}C nmr 41.0 (C-5), 42.2 (NCH_3), 47.0 (C-3), 54.7 (C-6), 61.3 (C-2), 113.8 (In-C7), 120.8 (In-C4), 123.4 (In-C5), 123.7 (In-C2), 125.2 (In-C6), 126.7 (Ar-*ortho*), 128.8 (Ar-*meta*), 129.3 (In-C3a) 133.9 (Ar-*para*), 135.6 (In-C7a), 137.9 (In-C3), 208.0 (C=O); ms (m/z, %) 368 (M^+, 25), 325 (6), 283 (10), 227 (100), 184 (25), 170 (29), 142 (40), 115 (28), 77 (33). Anal. Calcd for $C_{20}H_{20}N_2O_3S$: C, 65.22; H, 5.43; N, 7.61. Found: C, 65.40; H, 5.55; N, 7.89.

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